Individualized dosing in the treatment of RRMS using S1P receptor modulating therapies: a simulation study

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Introduction

- Over the past decade, several S1P receptor modulators (*a.k.a. x*-imods) have been brought into clinical development: fingolimod, siponimod, ONO-4641, CS-0777, ponesimod and RPC1063
- Except fingolimod which is a nonselective receptor agonist, these '*x*-imods' are targeting different subsets of the five S1P receptors ($S1P_1$ to $S1P_5$); yet, all these compounds share the same property of acting on the receptor $S1P_1$ involved in the regulation of lymphocyte trafficking.
- Down-regulation of lymphocytic S1P1 receptors by *x*-imods' leads to retention of self-reactive T cells in the lymph nodes and prevents their invasion of the CNS[1].
- In this family of compounds, the extent of drug effect on lesion count is assumed to be correlated to the one on lymphocytes. On average, the disease burden is expected to be reduced in patients with decreased absolute peripheral lymphocyte counts.
- Assessing the variability of lymphocyte response to treatment is critical in order to avoid
  - SAE *e.g.* severe lymphopenia and infection, if the lymphocytes are too low,
  - Failure due to lack of efficacy, if the lymphocytes remain too high.
- Using retro-engineering, it is possible to determine a target lymphocyte window to which would correspond a certain level of efficacy as measured by reduction in relapse or lesion counts.
- Lymphocyte measurement is a standard procedure which can be performed early-on during the conduct of a clinical trial. Based on lymphocyte readout, it would be possible to adjust the dose regimen of a patient in order to bring her/him in the desired target lymphocyte window.

- **The objective of this work** is to assess the feasibility and relevance of individual dose adjustment in patients treated with sphingosine-1-phosphate receptor modulators (*x*-imods) based on peripheral lymphocyte counts.

From dose to relapse

- It has been observed in various clinical trials that, as *x*-imod dose increases, lymphocytes, lesion counts and relapse occurrence decrease (**Figure 1**).
- The estimates for maximum reduction (I_{max}) in lymphocyte levels are similar across *x*-imods (**Table 1**). The main difference between these compounds resides in their potency, *i.e.* the concentration required to reach 50% of the maximum effect (*a.k.a.* EC50).
- The relationship between lymphocytes and lesion counts is *drug-independent*[7]. This is also the case for the correlation between lesion count and relapse[8]. Here, it is *assumed* that the only force driving the drug effect on this framework is the one relating the drug dose/concentration to lymphocytes.
- From **Figure 1C**, it could be argued that a dose bringing the average lymphocyte count into the window of **0.2 to 0.5 x10E9/L** would drag the average lesion count below 0.5 *i.e.* convey a ~80% reduction.
- The individual-level response-time profiles would be much more erratic and heterogeneous than the central tendency described in **Figure 1**, as they would be perturbed by:
  - Patient-specific intrinsic and extrinsic factors affecting the pharmacokinetics and the response to treatment,
  - Measurement error and unexplained variability.
- As a consequence, a significant portion of patients treated with *x*-imods could have their lymphocyte level at steady state (reached ~2 weeks after treatment initiation) falling outside the target window of 0.2-0.5 x10E9/L.

Table 1: Estimates for maximum reduction (I_{max}) of lymphocyte levels at steady state

Typical values	I_{max} (%)
CS-0777[5]	85
Fingolimod[2]	87
ONO-4641[3]*	83
Ponesimod[6]	94
Siponimod[4]	83

*Predicted from animal preclinical study data

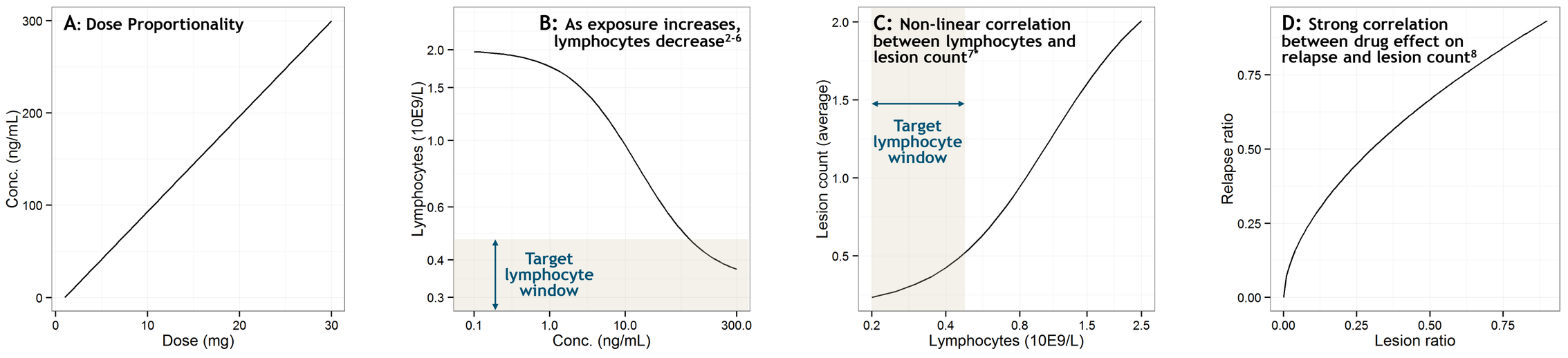

Figure 1: Key relationships involved in the mechanism of action of S1P-receptor modulators. A change in dose would cascade throughout these chained effects.

*Illustration for the case of patients with at least one Gd+ lesion at baseline

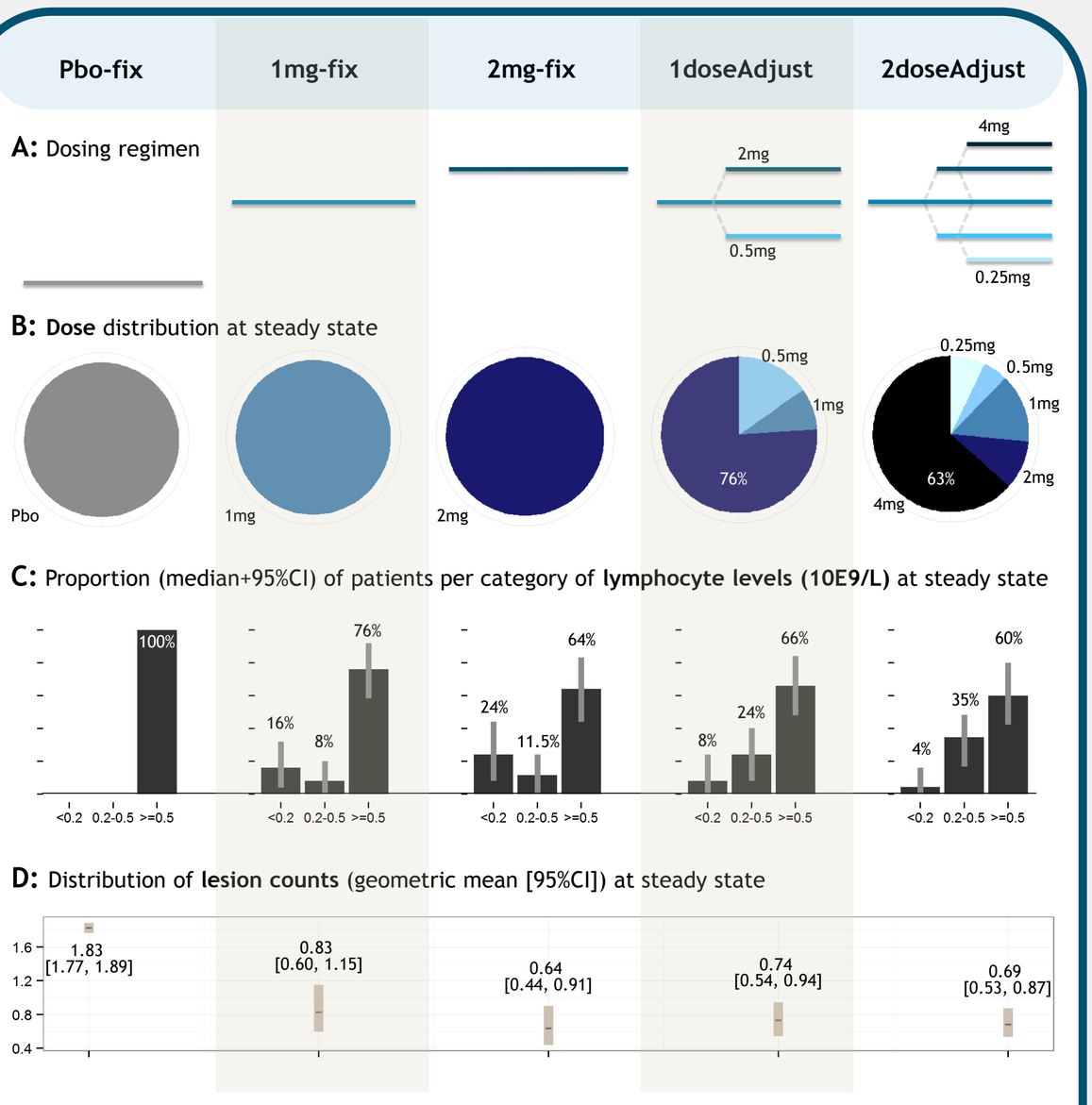

Figure 2: Effect of individualized dosing regimen (**A, B**) on lymphocyte (**C**) and lesion count (**D**) distributions, based on simulations of 200 trials including 50 patients per arm.

Individual dose adjustment

- A solution to increase the proportion of patients with lymphocyte levels within the desired target window at steady state is to allow for dose adjustment. The aim of this dosing strategy would be to improve the treatment benefit-risk ratio as compared to a fixed-dose regimen by:
  - Increasing the efficacy, in pulling the lymphocytes levels of 'non-responder' subjects below 0.5 x10E9/L thanks to dose increases,
  - Limiting the safety risk, in shortening as much as possible the time spent with lymphocytes below 0.2 x10E9/L thanks to dose reductions.

Simulations

- The principles used in this simulation exercise could be applicable to any *x*-imod.
- Five dosing scenarios are considered: three fixed dose regimen (placebo, 1 mg, 2 mg) and two flexible dosing regimen (**Figure 2A**).
- Simulations of PK and lymphocyte time course were run for 200 trials including 25 patients each. Individual lymphocyte-time profiles were generated computationally (using the Pharsight TrialSimulator®, TS2) using the siponimod PKPD model[4]. The lesion counts were derived from the equation used in **Figure 1C**.
- The simulation results were expressed in terms of:
  - Distribution of doses at steady state (**Figure 2B**),
  - Proportion of patients with lymphocyte levels above or below predefined cut-offs, at steady state (**Figure 2C**),
  - Distribution of lesion counts (**Figure 2D**).
- *Note*: As a working assumption, the calculation of mean lesion count relies on the idea that the totality of the clinical benefit is conveyed through the drug effect on lymphocyte levels. This is a recognized strong assumption of this simulation exercise.

Key results

- When dose adjustment is allowed, a large proportion of patients have their dose increased to reach the target window of lymphocyte counts (0.2-0.5 x10E9/L).
- The proportion of patients with lymphocyte<0.2 x10E9/L is dropping from 24% in the 2 mg-fix scenario to less than 5% in the 2doseAdjust scenario.
- The mean lesion count obtained in the 2doseAdjust scenario (0.69 [0.53, 0.87]) is equivalent to the one obtained in the 2mg-fix scenario (0.64 [0.44, 0.91]).

Conclusions

- Fixed-dose regimens assume that all patients are equal. However, patients are different the ones from each other, and therefore should receive dose adapted to their need. A simulation study shows how RRMS patients treated with *x*-imods could benefit from individualized dosing.
- Benefit of dose adjustment: The proportion of patient exposed to higher risk of infection due to severe lymphopenia (<0.2 x10E9/L) is reduced from 24% (with a fixed daily dose of 2 mg) to less than 5% (with dose adjustment), while the benefit on efficacy endpoint (lesion count) is maintained.

References

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